Dispatches

Aging: Filtering Out Bad Mitochondria

During yeast cytokinesis an aged mother cell gives rise to an immaculate daughter cell. A new study now demonstrates that this rejuvenation encompasses a novel Sir2- and actin-cable-dependent filtering process that prevents feeble mitochondria from entering the daughter cell.

Thomas Nyström

Asymmetric cell division is key to cellular differentiation and cell renewal [1]. For example, the budding yeast *Saccharomyces cerevisiae* utilizes asymmetrical division to generate a young daughter cell from a mother cell that grows progressively older with each cell division and finally perishes; the hallmark of replicative aging. This singular division event provides a tractable model for how age physiognomies are reset in the progeny and show that the generation of a pristine daughter cell requires asymmetrical segregation and compartmentalization of cytoplasmic 'aging factors' [2–6]. Identification of such aging factors is one of the 'holy grails' of gerontology, as this might provide clues towards therapeutically halting, or even reversing, senescence and tissue decline.

Several findings have highlighted dysfunctional mitochondria as key aging factors, and such defective mitochondria accumulate in yeast mother cells during aging [7–9]. That the emergence of these dysfunctional mitochondria is not only a corollary but also a cause of aging is supported by the fact that mutations that reduce age-related mitochondrial fragmentation and malfunction extend the replicative lifespan of mother cells [7]. Moreover, proper segregation of mitochondria is required to establish cellular age asymmetry [10] and recent findings imply that this is coupled to daughter cells predominantly inheriting the mother cell's healthier mitochondria from the functionally heterogeneous population of these organelles [11,12]. Such results raise the fundamental questions of how the cell identifies healthy and unhealthy mitochondria and how the unhealthy ones are prevented from being inherited by the progeny. A new study by the Pon laboratory [13], published in this issue of *Current Biology*, now highlights that this is accomplished by a fascinating process of mitochondrial sifting that relies on retrograde movement of actin cables and the anti-aging protein Sir2.

To approach a possible filtering process, the authors first needed a way to distinguish between healthy and unhealthy mitochondria and used a mitochondria-targeted redox-sensing protein (mito-roGFP1) to quantify the state of mitochondrial oxidation. Their data support the notion that mitochondria displaying increased oxidation are less healthy/functional. Consistent with previous reports, the reduced and healthy mito-roGFP1-tagged mitochondria were enriched in the daughter cells after cytokinesis, suggesting that less vigorous mitochondria are subjected to some kind of filtering process [13].

To pin down the nature of such a filtering device, we must first reflect on how the daughter inherits mitochondria from its mother cell: a growing number of reports suggest that mitochondria are transferred to the daughter cell by the assistance of actin cables and the myosin V-type protein Myo2 [14]. Myo2, propelled by its motor force, moves in one direction on yeast actin cables — towards the daughter cell (Figure 1A,B). However, this movement is against a cable flow in the opposite direction (retrograde flow), towards the mother cell. This is because actin monomers are inserted into the growing actin cable at a site, called the polarisome, at the tip of the daughter cell, which pushes the cable 'backwards' towards the mother (Figure 1A,B). Thus, anything aspiring to enter the daughter cell on the actin-cable 'railway' track needs to move faster than the backward flow of the track. Realizing these facts, the authors, utilizing their mito-roGFP1 reporter, tested whether oxidized and reduced mitochondria moved on these tracks with similar or differential rates and found that reduced (i.e. robust and healthy) mitochondria moved faster against the flow.

This finding opens the possibility that unhealthy mitochondria are not traveling fast enough on the tracks to make it into the daughter before completion of cytokinesis. (For an analogy, think about an athletic person versus a couch potato trying to reach the end of a conveyor belt going in the wrong direction.) To test this, the authors asked whether altering the rate of cable counter-flow affected the inheritance of bad mitochondria and found that it did. Explicitly, by reducing the rate of retrograde cable flow (via a *myo1* mutation) more unhealthy mitochondria reached the daughter cell while increasing retrograde flow (via a *tpm2* mutation) caused the opposite, i.e. an even more pronounced enrichment of healthy mitochondria in the daughter cell. Remarkably, increasing the inheritance of healthy mitochondria by speeding up retrograde flow extended replicative lifespan. This lifespan extension was no longer seen in cells lacking mitochondrial respiration, suggesting that retarding aging by elevating actin cable flow is truly linked to mitochondrial function and a boost in mitochondrial sifting.

The deacetylase and anti-aging protein Sir2 has previously been shown to affect actin-cable abundance and cytoskeletal functions [15,16]. This prompted the authors to test whether Sir2 dosage affected the inheritance of unhealthy mitochondria. Indeed, they first confirmed that Sir2-deficient cells harbor fewer actin cables and extended this analysis to show that the removal of *SIR2* decreased the velocity of actin flow and retrograde mitochondrial movement. This, in turn, allowed the less vigorous mitochondria to make it into the daughter cells. Overproduction of Sir2 had the exact opposite effect. These results are consistent with data demonstrating that Sir2 affects the rate of actin folding by modulating the activity of the chaperonin CCT [16]. Thus, Sir2

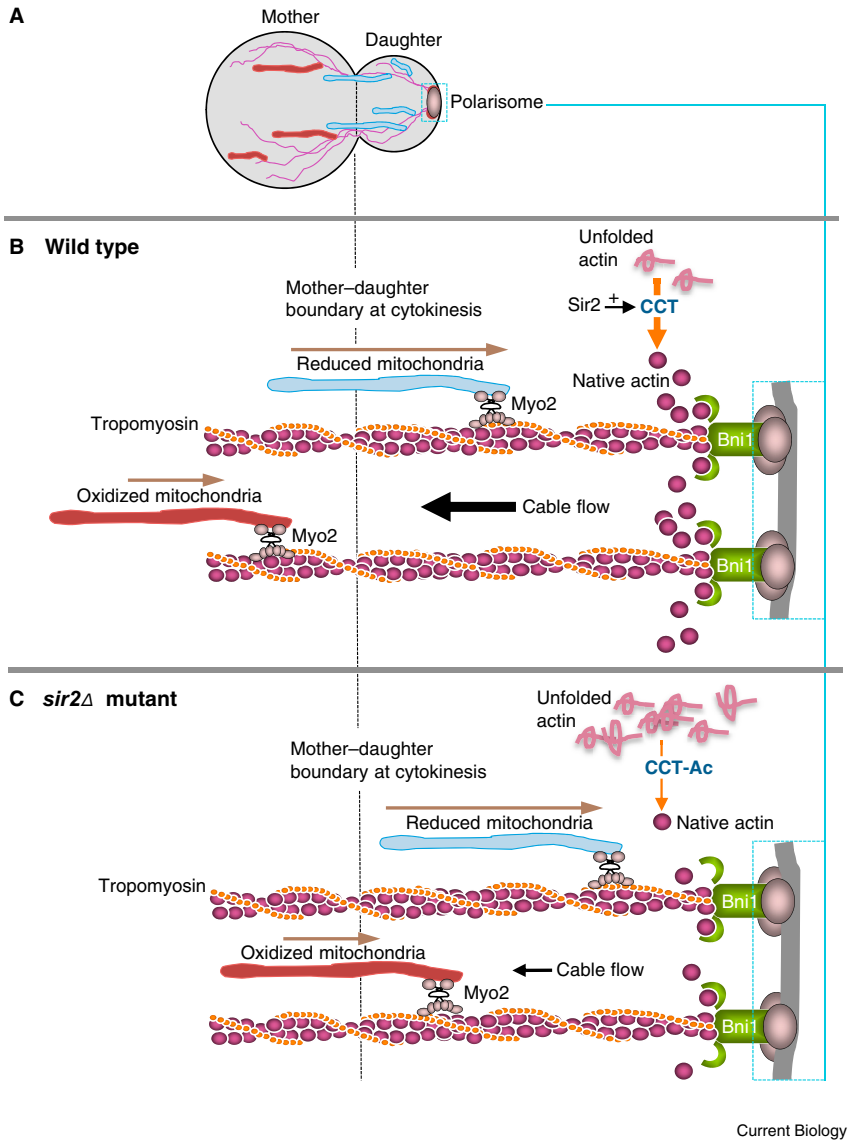

Figure 1. Schematic image of the process of mitochondrial sifting.

(A) A budding event with a mother cell giving rise to a daughter cell, which predominantly inherits reduced (blue) rather than oxidized (red) mitochondria transported on actin cables. (B) Retrograde actin flow is achieved by actin nucleation by the Bni1 formin at the polarisome complex at the tip of the daughter cell. Mitochondria using the myosin motor protein Myo2 to reach the daughter are therefore moving against the flow, and less mobile mitochondria (oxidized; red) are less likely to reach the daughter before completion of cytokinesis. The substrate of the polarisome — properly folded actin — is provided by the chaperonin CCT, the activity of which, in turn, is modulated by Sir2 [16]. (C) Cable retrograde flow is reduced in a cell lacking Sir2 [13], possibly as a consequence of limited availability of folded actin monomers [17], allowing the less motile and oxidized mitochondria to reach the daughter.

deficiency might limit the availability of substrates — properly folded actin — for the polarisome, resulting in diminished actin nucleation at the bud tip, reduced retrograde actin flow, and increased inheritance of oxidized and unhealthy mitochondria (Figure 1B,C). These findings are intriguing also in view of the fact that dysfunctional mitochondria trigger increased Sir2-dependent genomic silencing [17]. This enhanced Sir2 activity, like mild Sir2 overproduction [13], might increase the retrograde flow of actin cables, ensuring that the filtering process is boosted upon demand, i.e. when imminent mitochondrial decline is sensed. Remarkably, Sir2 has now been linked to the management of no less than three aging factors in yeast: extrachromosomal rDNA circles [3], aggregated proteins [6,17], and now dysfunctional mitochondria [13]. For at least two of these aging factors — aggregated proteins and dysfunctional mitochondria — Sir2 acts by restricting their transfer to daughter cells in an actin-cable-dependent manner.

There are always a number of stimulating questions arising from new and important discoveries. Concerning the mitochondrial filtering process, it would be interesting to learn the mechanistic rationale behind the differential velocity of reduced and oxidized mitochondria. Is the redox state of the mitochondria affecting Myo2 motor activity, force generation, and/or the stability of mitochondria–Myo2 interactions through adaptor proteins? Are the fragmented mitochondria of old mother cells effectively filtered by this process or is quality control hampered by unbalanced mitochondrial fission? Since budding yeast upholds most, if not all, its organelle inheritance using actin cables and class V myosins (Myo2 and Myo4), one also wonders whether other organelles are subjected to a similar quality control mechanism depending on actin counter-flow as has been reported here to operate on mitochondria. If so, might there be a trade-off between or a hierarchy among organelle quality control systems due to the fact that different organelle adaptor proteins compete for Myo2 binding [18]? Another question is to what extent this filtering process operates in other organisms. Retrograde actin flow also drives organelle movement in higher eukaryotes, including mammals, and has been observed in lamellipodia, dendritic spines, immunological synapses and filopodia. A retrograde flow of actin might therefore be involved in selecting organelles of differential capacity for conveyance to discrete regions. Alternatively, filtering processes in higher organisms might be more reliant on microtubules, a possibility that could be worth pursuing. With respect to Sir2, it would be interesting to learn whether the role of this sirtuin in mitochondrial quality control is evolutionarily conserved and, if so, whether asymmetrical segregation of dysfunctional mitochondria, like oxidized proteins [19,20], is required for safeguarding the fitness of one

cell lineage at the expense of the other during stem/progenitor cell renewal.

References

1. Knoblich, J.A. (2008). Mechanisms of asymmetric stem cell division. Cell *132*, 583–597.
2. Egilmez, N.L., and Jazwinski, S.M. (1989). Evidence for the involvement of a cytoplasmic factor in the aging of the yeast Saccharomyces cerevisiae. J. Bacteriol. *171*, 37–42.
3. Sinclair, D.A., and Guarente, L. (1997). Extrachromosomal rDNA circles - a cause of aging in yeast. Cell *91*, 1033–1042.
4. Hughes, A.L., and Gottschling, D.E. (2012). An early age increase in vacuolar pH limits mitochondrial function and lifespan in yeast. Nature *492*, 261–265.
5. Aguilaniu, H., Gustafsson, L., Rigoulet, M., and Nyström, T. (2003). Asymmetric inheritance of oxidatively damaged proteins during cytokinesis in *Saccharomyces cerevisiae*: a Sir2p dependent mechanism. Science *299*, 1751–1753.
6. Erjavek, N., Larsson, L., Grantham, J., and Nyström, T. (2007). Accelerated aging and failure to segregate damaged proteins in Sir2 mutants can be suppressed by overproducing the protein aggregation-remodeling factor Hsp104p. Genes Dev. *21*, 2410–2421.
7. Scheckhuber, C.Q., Erjavec, N., Tinazli, A., Hamann, A., Nyström, T., and Osiewacz, H.D. (2007). Reducing mitochondrial fission results in both increased life span and fitness of two fungal ageing models. Nat. Cell Biol. *9*, 99–105.
8. Veatch, J.R., McMurray, M.A., Nelson, Z.W., and Gottschling, D.E. (2009). Mitochondrial dysfunction leads to nuclear genome instability via an iron-sulfur cluster defect. Cell *137*, 1247–1258.
9. Erjavec, N., Bayot, A., Gareil, M., Camougrand, N., Nyström, T., Friguet, B., and Bulteau, A.L. (2013). Deletion of the mitochondrial Pim1/Lon protease in yeast results in accelerated aging and impairment of the proteasome. Free Radic. Biol. Med. *56*, 9–16.
10. Lai, C.Y., Jaruga, E., Borghouts, C., and Jazwinski, S.M. (2002). A mutation in the *ATP2* gene abrogates the age asymmetry between mother and daughter cells of the yeast *Saccharomyces cerevisiae*. Genetics *162*, 73–87.
11. McFaline-Figueroa, J.R., Vevea, J., Swayne, T.C., Zhou, C., Liu, C., Leung, G., Boldogh, I.R., and Pon, L.A. (2011). Mitochondrial quality control during inheritance is associated with lifespan and mother-daughter age asymmetry in budding yeast. Aging Cell *10*, 885–895.
12. Klinger, H., Rinnerthaler, M., Lam, Y.T., Laun, P., Heeren, G., Klocker, A., Simon-Nobbe, B., Dickinson, J.R., Dawes, I.W., and Breitenbach, M. (2010). Quantitation of (a) symmetric inheritance of functional and of oxidatively damaged mitochondrial aconitase in the cell division of old yeast mother cells. Exp. Gerontol. *45*, 533–542.
13. Higuchi, R., Vevea, J.D., Swayne, T.C., Chojnowski, R., Hill, V., Boldogh, I.R., and Pon, L.A. (2013). Actin dynamics affects mitochondrial quality control and aging in budding yeast. Curr. Biol. *23*, 2417–2422.
14. Vevea, J.D., Swayne, T.C., Boldogh, I.R., and Pon, L.A. (2013). Inheritance of the fittest mitochondria in yeast. Trends Cell Biol. http://dx.doi.org/10.1016/j.tcb.2013.07.003, doi:pii: S0962–8924(13)00114-1.
15. Erjavec, N., and Nyström, T. (2007). Sir2p-dependent protein segregation gives rise to a superior reactive oxygen species management in the progeny of Saccharomyces cerevisiae. Proc. Natl. Acad. Sci. USA *104*, 10877–10881.
16. Liu, B., Larsson, L., Caballero, A., Hao, X., Öling, D., Grantham, J., and Nyström, T. (2010). The polarisome is required for segregation and retrograde transport of protein aggregates. Cell *140*, 257–267.
17. Caballero, A., Ugidos, A., Liu, B., Öling, D., Molin, M., Kvint, K., Hao, X., Mignat, C., Nachin, L., Molin, M., and Nyström, T. (2011). Absence of mitochondrial translation control proteins extend life span by activating sirtuin-dependent silencing. Mol. Cell *42*, 390–400.
18. Eves, P.T., Jin, Y., Brunner, M., and Weisman, L.S. (2012). Overlap of cargo binding sites on myosin V coordinates the inheritance of diverse cargoes. J. Cell Biol. *198*, 69–85.
19. Rujano, M.A., Bosveld, F., Salomons, F.A., Dijk, F., van Waarde, M.A., van der Want, J.J., de Vos, R.A., Brunt, E.R., Sibon, O.C., and Kampinga, H.H. (2006). Polarised asymmetric inheritance of accumulated protein damage in higher eukaryotes. PLoS Biol. *4*, e417.
20. Bufalino, M.R., Deveale, B., and van der Kooy, D. (2013). The asymmetric segregation of damaged proteins is stem cell-type dependent. J. Cell Biol. *201*, 523–530.

Department of Chemistry and Molecular Biology, University of Gothenburg, Medicinaregatan 9C, S-413 90 Göteborg, Sweden.
E-mail: Thomas.nystrom@cmb.gu.se

http://dx.doi.org/10.1016/j.cub.2013.10.049

Body Perception: Intersensory Origins of Self and Other Perception in Newborns

Self-perception involves integrating changes in visual, tactile, and proprioceptive stimulation from self-motion and discriminating these changes from those of other objects. Recent evidence suggests even newborns discriminate synchronous from asynchronous visual-tactile stimulation to their own body, a foundation for self-perception.

L.E. Bahrick

> *"Information about the self accompanies information about the environment, and the two are inseparable. Egoreception accompanies exteroreception, like the other side of a coin. Perception has two poles, the subjective and objective, and information is available to specify both. One perceives the environment and coperceives oneself"*
>
> J.J. Gibson [1] (p. 126)

The world provides a richly structured array of continuously changing multimodal stimulation to all our senses. Despite the fact that our information about the world is dynamic and arrives through distinct sensory channels, we perceive ourselves as coherent entities, situated in a stable world of unitary objects and events. How and when we develop the ability to coordinate stimulation across the senses such that we perceive the self and the objects and events in the world as distinct, unitary multimodal entities is a question that has intrigued philosophers and scientists for centuries, dating as far back as Aristotle. A recent study by Filipetti *et al.* [2], reported in this issue of *Current Biology*, adds a new piece to this puzzle. It suggests that a fundamental form of this ability is present in newborn infants. Newborns detect visual-tactile synchrony in movements directed to their own body and discriminate synchrony from visual-tactile asynchrony. Synchrony detection is known to be a cornerstone of perceptual development, a key to linking stimulation across the senses, and a foundation for distinguishing the self from other objects and events in the world [3,4].

The past several decades have witnessed an explosion of research on intersensory and synchrony perception, catalysed in large part by James and Eleanor Gibson's [1,5,6] ecological approach to perception and perceptual development. Instead of posing a problem for perception, as argued by prevailing theories, the Gibsons proposed that the different forms of sensory stimulation and their overlap provide an important basis for perceiving a unified self situated in a world of unified multimodal objects and events. The senses work in concert